EXHIBIT C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 8 Cases*	

Expert Report of C. Bryce Bowling, MD, FACOG, FACS, FPMRS on Gynecare TVT / TVT Exact / TVT-O

I. CREDENTIALS & QUALIFICATIONS

My name is Chadwick Bryce Bowling. My curriculum vitae (CV) attached hereto as Exhibit A reflects my education, training and unique qualifications to render an opinion on Ethicon's TVT/TVT-Exact & TVT-O. I am a Urogynecologist / Pelvic Reconstructive Surgeon. A "urogynecologist" is a gynecologist with advanced training and education in the evaluation and treatment of women with complex pelvic floor issues, including urinary and bowel incontinence complaints and pelvic prolapse/relaxation defects. I treat individuals with the above-mentioned problems, as well as those with pelvic pain syndromes, urinary and defecatory

voiding dysfunction, interstitial cystitis, childbirth injuries, genital tract fistulas, and I have extensive expertise in correcting serious mesh complications.

I am a *Summa Cum Laude* graduate of the University of Tennessee, Knoxville with a Bachelor in Sciences obtained in 1998. I obtained my MD from the University of Tennessee Health Sciences Center in Memphis, TN in 2003. I completed an internship and residency in Obstetrics & Gynecology at The Regional Medical Center in Memphis, where I served as Chief Resident. Following my residency in Obstetrics & Gynecology, I completed a fellowship in Female Pelvic Medicine and Reconstructive Surgery at The University of Alabama at Birmingham, under the supervision of internationally recognized Urogynecologists Dr. Ed Varner and Dr. Holly Richter. The fellowship was three years in length and accredited both by the American Board of Urology and the American Board of Obstetrics and Gynecology.

After completing my fellowship, I accepted a position as Assistant Professor of Obstetrics & Gynecology at The University of Tennessee Medical Center in Knoxville, TN, where I established the Division of Urogynecology.

I am Board Certified in both Obstetrics & Gynecology and Female Pelvic Medicine & Reconstructive Surgery. I am a Fellow of the American College of Obstetricians and Gynecologists, a Fellow of the American College of Surgeons, and a Diplomate of the American Board of Obstetrics & Gynecology.

I am a member of several societies who strive to improve the overall health and quality of life in women, including the American Urogynecologic Society (AUGS), Society of Gynecologic Surgeons (SGS), and the International Continence Society (ICS). I have published numerous journal articles, as well as book chapters in the fields of Gynecology and Urogynecology, have presented my

research findings at both national and international conferences on women's pelvic health, and have travelled to African nations volunteering medical services to women with life-altering gynecologic issues without access to routine healthcare.

I currently serve as Director for the Division of Female Pelvic Medicine and Reconstructive Surgery at The University of Tennessee Medical Center in Knoxville, TN, where I practice 5 days per week, varying my time between in-office evaluation, non-surgical and surgical management of patients with pelvic floor defects, as well as education of medical students, residents, and other faculty physicians.

Throughout my career, I have performed thousands of pelvic floor reconstructive procedures to treat and cure pelvic organ prolapse, urinary incontinence, fecal incontinence and multiple other pelvic floor issues, and have extensive experience in dealing with complications that arise from each. I am proficient in correcting pelvic organ prolapse both with and without the use of mesh, including abdominal, laparoscopic and robotic sacral colpopexy, vaginal hysterectomy, intraperitoneal and retroperitoneal uterosacral vault suspension, sacrospinous ligament fixation, colporrhaphy and hysteropexy. I am also proficient in the use of mid-urethral slings for the treatment of stress and mixed urinary incontinence and continue to use those weekly in my management of patients seeking more definitive treatment options. I am also trained in the use of and commonly perform neuromodulation procedures for the treatment of urge urinary and fecal incontinence.

In addition to surgical management, my expertise extends to the daily use of diagnostic testing for urinary and fecal incontinence including simple and complex urodynamic assessments, in-office cystoscopy, anorectal manometry, and endoanal ultrasound. I devote a significant amount of my day seeing patients with both stress

and urge incontinence, voiding dysfunction, urinary retention, recurrent urinary tract infections, and surgical complications leading to fistulae.

I am considered one of the leading experts in the southeastern United States region for native tissue repairs, mesh augmented prolapse procedures, anti-incontinence procedures, as well as surgical revision of complications related to vaginal mesh implant procedures.

I have trained with and performed the Gynecare TVT procedures since 2004 and have successfully completed over 2000 retropubic sling procedures since that time. I have also performed hundreds of transobturator slings.

I trained with and performed the Gynecare Prolift procedure in excess of 500 times (Anterior, Posterior and Total) beginning in 2007 and continuing until their production was halted in 2012, and contend, to this day, that the Prolift system was the single best vaginal approach prolapse repair kit ever available.

I have extensive knowledge of pelvic floor anatomy and have taught pelvic floor anatomy courses via the use of cadavers to both residents and faculty members, both at The University of Alabama at Birmingham and The University of Tennessee Medical Center in Knoxville.

I incorporate my extensive knowledge of pelvic floor anatomy, diagnostic skills, surgical and non-surgical treatment of pelvic floor abnormalities, and, specifically, my knowledge of Ethicon's TVT/TVT-Exact & TVT-O into this report. All of my opinions are held to a reasonable degree of medical and scientific certainty. I reserve the right to amend this report and my opinions pending receipt of additional materials.

II. MATERIALS REVIEWED

In preparing this expert report, I have performed an exhaustive study of the scientific literature including Cochrane reviews, ACOG Committee Opinions, Position Statements from the major gynecologic surgical societies, randomized controlled trials (RCTs) and peer-reviewed research studies of the highest caliber, detailing decades of opinions and scientific findings in the treatment of stress urinary incontinence including surgical and nonsurgical repairs, via both mesh augmented repairs and native tissue repairs. In addition to the medical literature cited at the end of this report, I have also performed a review of Ethicon's surgeon resource monograph, professional education materials and the TVT instructions for use. I have reviewed the expert statements of multiple Plaintiff's Experts for both case specific and general reports. Additionally, with almost 15 years of experience utilizing and inserting Gynemesh materials in the treatment of prolapse and incontinence, I have chosen to incorporate years of personal experience in the diagnosis and treatment of stress urinary incontinence as well as associated complications.

III. FEES

My hourly rate for review of materials and drafting this report is $600.00. Deposition fees are $4000.00 for up to 4 hours and $6000.00 exceeding 4 hours + any additional travel expenses. Fees for trial testimony are $7500.00 daily + any additional travel expenses.

IV. EXPERT OPINION

I hold the following opinions to a reasonable degree of medical and scientific certainty. All opinions have been compiled based on my education, training and professional experience as a gynecologic surgeon. Additionally, I utilize my significant background in evaluating, diagnosing and treating women with pelvic floor pathologies, annual participation in national and international meetings on women's pelvic health, as well as an extensive review of the available medical literature as it pertains to stress urinary incontinence treatment, including surgical and non-surgical strategies. I reserve my right to amend or supplement this opinion based on new information that becomes available.

A. Background of Stress Urinary Incontinence

In order to properly discuss the treatment strategies of stress urinary incontinence one must have an appreciation of the anatomic components that lead to the continence mechanism, continence mechanism functions, and to understand how and why these functions break down. If the intraurethral pressure exceeds the pressure generated inside the bladder during times of straining and valsalva, continence is maintained. Under normal circumstances, the urethral sphincter keeps the urethra closed via its normal contraction while the detrusor muscle of the bladder stays in a relaxed state allowing the bladder to fill normally. Once the bladder is at a volume that can provide a sustainable detrusor contraction, a near simultaneous relaxation of the urethral sphincter and contraction of the detrusor muscle occur in an attempt to empty the bladder's volume without valsalva assistance and without hindrances or obstructions. Coordination must occur between the bladder's detrusor muscle, urethral sphincter complex and the brain's neural signals in order for normal continence and normal micturition to proceed.

Most people take this complicated coordination for granted until they are faced with urinary incontinence, voiding dysfunction or potentially both.

There are a number of different factors that play into overall urinary incontinence but for the sake of discussion regarding TVT mid-urethral slings and their use in the treatment of incontinence, we will confine the discussion of incontinence mainly to stress urinary incontinence and will also touch a little bit on some of the mixed urinary incontinence components. As a general rule of thumb, stress urinary incontinence is considered to be an anatomic defect, whereas traditional urge urinary incontinence may or may not be caused by anatomic abnormalities. These anatomic defects that occur leading to the development of stress urinary incontinence typically revolve around damage done to the pubocervical and periurethral connective tissue layers that offer support to the urethra. The support structures of the urethra provide a platform, in essence, for the urethra to rest upon, so that activities that increase intra-abdominal pressure such as coughing, sneezing, exercise, valsalva maneuvers and even intercourse, can close the urethra down against its supportive platform thus closing off the urethra and increasing the intra-urethra pressure such that it exceeds the intra-detrusor pressure. As detailed above, this is how continence is maintained. A combination of increasing age, childbirth and/or connective tissue abnormalities, similar to those seen in pelvic organ prolapse patients, can lead to a weakening and attenuation, or an overall tear of the supportive structures underneath the urethra leading to an inability of the urethra to properly close and properly increase the intra-urethral pressure. As a result, when the intra-detrusor pressure generated by a cough, sneeze, laugh, exercise or similar valsalva conducted activity occurs, the involuntary loss of urine from the urethra will occur. This very involuntary loss of urine during Valsalva maneuvers is the classic definition of stress urinary incontinence.

The overall prevalence of stress urinary incontinence in the population has been estimated between 25 and 35% in well-respected clinical studies. (Markland 2011) This common and embarrassing condition affects 200 million people worldwide with an estimated prevalence around 27.6%. (Minassian VA, Drutz HP, Al-Badr A. Urinary incontinence as a worldwide problem. Int J Gynecol Obstet. 2003;82:327–338.)

Olsen (1997) provided the classically quoted 11% lifetime risk that a woman will undergo at least one operation for pelvic organ prolapse (herein after referred to as POP) or stress urinary incontinence (herein after referred to as SUI) in her lifetime. There is also known to exist, secondary to urinary incontinence, an overall financial cost to the US healthcare system of over $20 billion annually in the United States alone.

The presence of stress urinary incontinence can be quite debilitating to the affected woman. The presence of stress urinary incontinence can interfere with a woman's physical, psychological and social well-being. Another detriment to women with stress urinary incontinence is in the form of decreased sexual function and a lower sexual quality of life (QoL). Multiple studies have shown significant links between the presence of SUI, altered body image and sexual dysfunction (Felippe 2017, Mota 2017, Chu 2015). Felippe, et al (2017) showed in their study of over 350 women, that women with UI were more likely to be sexual abstinent than continent women. Furthermore, women with UI showed less sexual desire, sexual comfort, and sexual satisfaction than their case-controlled continent counterparts.

Many times, women can no longer tolerate their symptoms and seek assistance from gynecologic surgeons. Treatment strategies for symptomatic SUI are wide ranging, from simple monitoring, pelvic floor exercises (Kegels) and pessaries to vaginal approach, laparoscopic/robotic approach, and open approach surgical repairs with and without the use of mesh augmentation. The decision for the desired treatment is usually made based on the degree of severity each patient experiences. Women with infrequent or minimal volume stress incontinence may require no treatment at all, while others may choose to utilize exercises or pessaries to reduce the leakage and feel more confident about their self-image. Women with more frequent, higher volume or more bothersome stress incontinent episodes open the door to surgical repairs. While pelvic floor physical therapy (PFPT) has been shown useful and effective in decreasing overall urinary incontinence symptoms, the exercises cannot provide definitive therapy to the women who leak with valsalva secondary to prolonged periods of exercise, as there is a rapid decrease in pelvic floor contraction strength after a matter of seconds. While pessaries can be used for some with stress incontinence, issues of an enlarged genital hiatus, or patient discomfort may preclude their use.

B. Conservative/Non-Surgical Options

Conservative management of SUI includes weight loss, smoking cessation, pelvic floor muscle exercises (PFPT/Kegels), and mechanical devices such as a pessary. Exercise-mediated reduction of weight by only 8% can result in a nearly 50% decrease in the frequency of incontinence episodes (Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. N Engl J Med. 2009;360:481–490). The problem with weight loss is the needed

exercise to lose weight many times increases the very incontinence the woman is trying to treat. Smoking cessation obviously is a good choice but data has shown that not only are current smokers at significant risk for urinary incontinence, but also former smokers exhibit a two-fold increased risk of incontinence. (Bump Am J Obstet Gynecol. 1992 Nov;167(5):1213-8)

While PFPT has been shown safe and effective in reducing urinary incontinence rates in various studies, women with SUI do not have the ability to maintain a pelvic floor contraction during the entirety of a workout. Additionally, studies have shown that the degree of treatment success is dependent upon the degree and duration of treatment (Bø, 1990), while more recent studies have suggested there is no long-term benefit in treating SUI with PFPT. (Beyar, Neurourol Urodyn. 2017)

Ghadeer's 2018 systematic review looked at 16 years of pessary use in women with stress urinary incontinence and found that, "vaginal pessaries are very effective at managing SUI if they are fit properly and managed by frequent removals and regular checkups." As stated above, the inherent problems with pessaries for both POP and SUI is the need for frequent follow-up and the potential side effects of discomfort, vaginal discharge, odor, bleeding and expulsion. These potential side effects often time lead women to abandon their use opting for surgical intervention. A study by Sarma (BJOG 2009) showed that 56% of women utilizing pessaries for symptomatic prolapse experienced complications comprising bleeding, extrusion, severe vaginal discharge, pain and constipation. Only 14% continued with pessary use over the 6-year study period.

Additionally, some women are self-conscious about the use of a pessary. We attempt, in my practice, to utilize pessaries as a first-line therapy for symptomatic

stress incontinence. We find, many times however, that women, particularly those that are still sexually active, are opposed to the idea of a pessary and the long-term management that goes along with their use.

Difficulty with self-removal and insertion of pessaries also limit their widespread use. Older patients with stress urinary incontinence, sometimes lack the dexterity required to remove and insert their pessaries, requiring multiple trips per year to their physician for management. Women in this older age group also routinely exhibit vaginal atrophy unless they are on maintenance estrogen therapy. Therefore, women in this age group must not only manage their pessary, but also must keep the surrounding vaginal tissue healthy with applications of localized estrogens multiple times per week.

While pessaries can serve as a first-line therapy for some with symptomatic incontinence and prolapse, they carry complications and obstacles many women are not willing to endure.

C. Non-Mesh Surgical Options

Prior to the fortunate advent of mid-urethral slings several traditional non-mesh augmented surgical approaches served to support the bladder neck via either retropubic urethropexy or bladder neck suspension procedures.

Anterior Colporrhaphy with Kelly Plication**:**
This procedure is believed to work by reinforcing the pubocervical fascial support of the bladder and urethra, supporting the bladder, bladder neck and urethra,

thereby providing a needed platform for the urethra to compress against, thereby decreasing stress urinary incontinence. While the Kelly plication was utilized for years in conjunction with anterior repairs performed during pelvic organ prolapse procedures, it has fallen out of favor due to massively high recurrence rates. Thaweekul (2004) found not only high post-operative urinary retention rates in excess of 40%, but a 5-year recurrence rate of about 47%. Other studies have shown a nearly 35% failure rate at 12 months. (Sohbati, 2015)

Needle Urethropexies:

Bladder neck suspension procedures such as the Pereyra and the Stamey needle procedures were originally attractive alternatives to other native tissue repairs, seeking to be more minimally invasive compared to open abdominal procedures. They were simple to perform with a seemingly low risk of complications; however, multiple studies showed over time that the failure rates were not only higher, but the complications were much more common than originally expected. Complications from needle suspensions include exposure of sutures, granulation tissue, urethral/bladder neck erosions, pain and bleeding. Studies of various needle urethropexies showed overall complication rates in excess of 45%. (Bidmead. British Journal of Urology, 1998; Jones. Br J Urol, 1989)

A Cochrane systematic review concluded that needle urethropexies were less effective for urinary incontinence than abdominal surgery with a near 30% failure rate within the first year. (Glazaner, 2017) Suture pull-throughs leading to failures were noted by Varner et al to occur, especially in obese patients. (Varner. Am J Obstet Gynecol 1990;163:551-7)

With abdominal routes offering higher success rates, and eventual sling procedures offering not only higher success rates, but lower complications and lower morbidity, needle urethropexies fell out of favor.

MMK/Burch:

These procedures work by elevating the bladder neck and increasing the poor urethral closure pressure resulting from defective urethral mucosal coaptation. The theory behind these procedures came from Enhorning's work in 1961 where it was suggested that during a valsalva maneuver (coughing, sneezing, laughing, etc), pressure transmission from the abdomen to the urethra with an accompanying reduction in overall urethral closure pressure resulted in stress urinary incontinence (SUI). As a result, Burch and MMK procedures were formed in an effort to increase outflow resistance, thereby increasing urethral closure pressure during valsalva maneuvers. The overall success of Burch and MMK procedures is well known – Lapitan's systemic review from 2005 showed "within the first year of treatment, the overall continence rate is approximately 85-90%. After five years, approximately 70% patients can expect to be dry. Newer minimal access procedures like tension free vaginal tape (TVT) look promising in comparison with open colposuspension but their long-term performance is not known and closer monitoring of its adverse event profile must be done." (Lapitan, 2005)

Also well known, however, are the high complication rates associated with Burch and MMK procedures, which are traditionally performed through larger abdominal incisions, increasing the risks of serious and significant bleeding, infection, retroperitoneal hematoma, voiding dysfunction, de novo detrusor instability and pain.

Fascial Slings:

The use of autologous fascial slings require harvesting of a piece of the patient's rectus fascia which is utilized as the sling device. The disadvantages of autologous fascial sling include a longer operating time due to graft harvesting and the associated morbidities of the harvesting site such as bleeding, hematoma, infection and pain.

The overall success of autologous fascial slings is variable throughout the literature, with success rates ranging from the mid 40% range to around 90%, and while studies have demonstrated its superiority to the open abdominal procedures of Burch and MMK, complications limit its routine use today.

"The autologous fascial sling results in a higher rate of successful treatment of stress incontinence but also greater morbidity than the Burch colposuspension." (SISTEr trial, NEJM 2007)

While fascial slings showed a high efficacy, they also showed greater morbidity, but they opened the door to the possibility of more minimally invasive sling procedures that could allow similar or even higher efficacy rates than the open abdominal approach procedures like Burch and MMK, without the pain associated with such invasive procedures.

D. Mesh Augmented Surgical Options

The goal of surgical correction of stress urinary incontinence is to restore anatomic function, anatomy and support. While a number of surgical routes and procedures

are available in the armamentarium of the gynecologic surgeon, the ideal surgery should lead to long-term successful outcomes with minimal risks of recurrence and complication. While no surgery is without a risk of both, surgeons became frustrated with the high failure rates and high complication rates patients were experiencing with previously available repairs.

All of the above-mentioned procedures carry with them intraoperative and post-operative risks including infection, hemorrhage, hematoma, visceral injuries, pain, dyspareunia, wound complications, urinary tract injuries, post-operative voiding dysfunction, de novo urge urinary incontinence and lower urinary tract symptoms. These associated risks have been observed and discussed for decades.

In addition to the associated risks of complications, operative times and estimated blood loss with many of these procedures were astounding when compared to the gold standard mid-urethral slings of today. The SISTEr trial, a trial of over 650 women treated for genuine stress urinary incontinence, compared two of the more common, yet invasive, procedures – the autologous fascial sling and the Burch colposuspension. The average blood loss for each procured was 230-240 ml with average operative times exceeding two hours. Studies looking at mid-urethral slings have shown blood loss around 40 ml (Richter, Obstet Gynecol. 2011 Apr; 117(4): 913–921) and the procedure is commonly performed in 15-20 minutes by a skilled surgeon. Over the years, surgery to address SUI became less invasive with the advent of the mid-urethral sling – designed with an intent of decreasing overall complications.

As stated above, and differing from the proposed continence mechanisms of Burch and MMK procedures, mid-urethral slings serve to re-create mid-urethral support.

Ford's 2015 Cochrane review stated, **"**recent findings on the pathophysiology of urinary incontinence have demonstrated that mid-urethral support, provided by the pubo-urethral ligaments, also plays an important role in maintaining continence when the intra-abdominal pressure rises." (Ford 2015)

Cure rates for TVT range from 65% to 95%, with one study showing a 90% cure rate after 11 years. Mesh mid-urethral slings like the TVT have been proven to be an effective treatment for genuine stress urinary incontinence and can even treat women successfully with mixed urinary incontinence in some cases. Bang (2016) described the advantages of newer mesh slings, stating, "the advantages of synthetic slings include a consistent sling material quality, predictable handling properties, and the assurance of sterility. As no autologous tissue is required, the usage of a synthetic sling also eliminates any harvest site related morbidities and patients undergoing the procedure have a shorter operative time and hospital stay compared to autologous sling patients." (Res Rep Urol. 2016; 8: 11–20)

Polypropylene, the material make-up of the TVT, despite assurances from Plaintiff's Counsel, has been shown safe and effective for decades. Prolene polypropylene suture, the entity comprising the matrix of Gynecare TVT, TVT-Exact and TVT-O slings was deemed "safe and effective for use" by the FDA in 1969 (B.H. Minchew, MD, Director of the FDA's Bureau of Medicine). Since that time, polypropylene has been used extensively in not just urologic and gynecologic surgeries but surgeries throughout the body. Multiple clinical trials have demonstrated the overall safety of type I polypropylene (Rezapour 2001, Ulmsten 2001, Nilsson 2001).

After the success of TVT retropubic, Ethicon released TVT-O. While made of the exact same Prolene mesh material as TVT, TVT-O passed through the obturator space, thus almost rendering impossible a bladder perforation. While this passage carries a small risk of post-operative groin pain, long-term studies have demonstrated that this risk is extremely low in the long term. Liapis (2010, Angioli (2010) Groutz (2011), Cheng (2012), Serati (2013), Laurikainen (2014), Tammaa (2017), Song (2017) Montera (2017) and Abdel-Fattah (2017) all demonstrate the long-term patient satisfaction and relatively high subjective and objective cure rates and low complication rates associated with TVT-O. TVT-O is functionally the same product as TVT in terms of its function and design; it utilizes the same prolene mesh implant and has similar subjective and objective cure rates at 5 years in systematic reviews. It differs only in its route of trocar placement and the shape of the trocars which serve to further protect the bladder during placement. It is noted in numerous studies to have lower rates of bladder injury and lower rates of post-operative voiding dysfunction. When professional statements and studies regarding the TVT procedure are quoted, they are noted by researchers and trained pelvic reconstructive surgeons to remain applicable to the TVT-O as well.

E. Systematic Reviews/Research

Cochrane Reviews measure benefits and harms by collecting data from more than one trial and combining them to generate an average result. This aims to provide a more precise estimate of the effects of an intervention and accomplishes this while reducing uncertainty. Cochrane meta-analyses offer a comprehensive review of randomized controlled trials (RCTs). They offer the highest level of clinical

evidence (Level I) and are considered to be the most reliable source of evidence to guide clinical practice.

In addition to multiple studies including RCTs, we will include Cochrane reviews in this discussion on recurrences. In doing so, I hope to paint a picture of what today's landscape is regarding mesh in the surgical correction of SUI.

Novara et al published a 2010 systematic review and meta-analysis looking at the comparative data on Burch colposuspension, pubovaginal / fascial slings and mesh mid-urethral slings in the surgical treatment of stress urinary incontinence. Their analysis included 39 randomized controlled trials (RCTs) comprised from nearly 16,000 patients. Novara's findings included the following:

- Patients receiving mid-urethral tapes had significantly higher overall (odds ratio [OR]: 0.61; confidence interval [CI]: 0.46–0.82; p = 0.00009) and objective (OR: 0.38; CI: 0.25–0.57; p < 0.0001) cure rates than those receiving Burch colposuspension, although they had a higher risk of bladder perforations (OR: 4.94; CI: 2.09–11.68; p = 0.00003).
- Patients undergoing mid-urethral tapes and pubovaginal slings had similar cure rates, although the latter were slightly more likely to experience storage lower urinary tract symptoms (LUTS) (OR: 0.31; CI: 0.10–0.94; p = 0.04) and had a higher reoperation rate.
- Patients treated with retropubic mid-urethral slings had slightly higher objective cure rates (OR: 0.8;CI: 0.65–0.99; p = 0.04) than those treated with TOT; however, subjective cure rates were similar, and patients treated with TOT had a much lower risk of bladder and vaginal perforations (OR: 2.5;

CI: 1.75–3.57; p < 0.00001), hematoma (OR: 2.62; CI: 1.35–5.08; p = 0.005), and storage LUTS (OR: 1.35; CI: 1.05–1.72; p = 0.02).

- most of the complications reported in the available RCTs were intraoperative ones, with a limited number of studies providing data on the intermediate- and long-term functional sequelae. That is of outmost importance because some underreported complications, including storage and voiding LUTS (seen more commonly in Burch and pubovaginal slings), can be disabling for the affected patients, whereas some intraoperative complications such as bladder injury during placement of retropubic mid-urethral slings are of little or no implication provided they are promptly recognized and treated.

To put it simply, mid-urethral slings (MUS) showed similar or higher efficacy rates compared to the more invasive Burch and pubovaginal sling procedures. And even though MUS showed a higher rate of bladder perforations, those are easily managed with little to no long-term sequalae compared to the more common complications from Burch and fascial slings of voiding dysfunction, UUI and LUTS symptoms, which are typically long-term and can be quite disabling for patients.

Ogah's 2011 short version Cochrane Review included 62 RCTs comprised of over 7000 participants surgically treated for their SUI. Ogah's key findings are as follows:

- Minimally invasive synthetic suburethral sling operations (like TVT and TVT-O) appeared to be as effective as traditional suburethral slings [8 trials, n = 599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94--1.13] but

with shorter operating time and less post-operative voiding dysfunction and de novo urgency symptoms.

- Minimally invasive synthetic suburethral sling operations (like TVT and TVT-O) appeared to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at 5 years RR 0.91, 95% CI: 0.74--1.12) with fewer perioperative complications, less post-operative voiding dysfunction, shorter operative time, and hospital stay, but significantly more bladder perforations (6% vs. 1%, RR 4.24, 95% CI: 1.71--10.52) (*expected when comparing an open abdominal incision with a trocar guided system*).
- Minimally invasive synthetic suburethral sling operations (like TVT and TVT-O) had significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities.
- A retropubic bottom-to-top route (like TVT) was more effective than top-to-bottom route (RR 1.10, 95% CI: 1.01--1.20; RR 1.06, 95% CI: 1.01--1.11) and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions.
- Monofilament tapes (like TVT and TVT-O) had significantly higher objective cure rates (RR 1.15, 95% CI: 1.02--1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06--1.00).
- The obturator route was less favorable than the retropubic route in objective cure (84% vs. 88%; RR 0.96, 95% CI: 0.93--0.99; 17 trials, n = 2,434), although there was no difference in subjective cure rates. However, there was less voiding dysfunction, blood loss, bladder perforation (0.3% vs. 5.5%, RR 0.14, 95% CI: 0.07--0.26), and shorter operating time with the obturator route.

Overall, the study concluded that when comparing mesh mid-urethral slings (like TVT and TVT-O), pubovaginal fascial slings and Burch colposuspension, "the current evidence base suggests that minimally invasive synthetic suburethral sling operations are as effective as traditional suburethral slings, open retropubic colposuspension and laparoscopic colposuspension in the short-term but with less postoperative complications."

Schimpf et al published a 2014 systematic review and meta-analysis comprised of over 20 years of scientific studies with minimum 12-month follow-ups comparing the long-term effectiveness of various interventions for surgical correction of SUI. The evidence favored the use of mesh mid-urethral slings over pubovaginal fascial slings. The same analysis showed that the more minimally invasive mesh mid-urethral sling showed similar efficacy to the more invasive Burch urethropexy.

Ford et al published a 2015 Cochrane review analyzing 81 trials consisting of over 12,000 women. After an extensive analysis of the data, Ford et al concluded, "Mid-urethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI."

Fusco et al published a 2017 systematic review and meta-analysis looking at the comparative data on Burch colposuspension, pubovaginal / fascial slings and mesh mid-urethral slings in the surgical treatment of stress urinary incontinence. Their

analysis included 28 randomized controlled trials (RCTs) comprised from nearly 16,000 patients. Fusco's findings included the following:

- Patients receiving mid-urethral slings (MUS) have significantly higher overall and objective cure rates than those receiving Burch colposuspensions.
- Similarly, there was a trend towards more favorable outcomes with MUS compared with laparoscopic Burch colposuspensions in all subanalyses.
- Patients undergoing mid-urethral slings and pubovaginal slings had similar cure rates.
- Patients treated with retropubic mid-urethral slings had higher subjective and objective cure rates than those receiving transobtuator slings.
- No significant differences in efficacy were identified comparing inside to out and outside to in transobturator slings.

Although similar cure rates were found between mid-urethral slings and pubovaginal slings, there was evidence in favor of mid-urethral sling for reoperation rates compared to pubovaginal sling although it did not read statistical significance. This reconfirms previous statistically significant lower reoperation rates in the mid-urethral sling groups compared to pubovaginal slings as demonstrated above. (Fusco 2017)

F. Other RCTs/Long Term Studies

The number of available long-term safety and efficacy data on TVT and TVT-O is astounding. The following is a mere sample of the available scientific literature

addressing both TVT and TVT-O slings in terms of their lasting efficacy and low complication rates.

Heinonen (2012) – Heinonen et al sought to evaluate the long-term outcome of the tension-free vaginal tape procedure. A total of 191 patients were operated on with tension-free vaginal tape between January 1998 and May 2000. Of these, 127 (66%) had stress urinary incontinence, 64 (34%) had mixed urinary incontinence and 39 (20%) had recurrent incontinence. A total of 138 (72%) of 191 patients were evaluated long-term using validated questionnaires to assess subjective cure and supine valsalva stress tests were utilized to assess objective cure rates (defined as a negative cough stress test and no need for a reoperation for SUI). The mean time of follow-up after their TVT sling was 10.5 years. The objective and subjective cure rates were 90% and 78%, respectively.

Out of the 138 patients followed for 10.5 years, only 3 had late-onset adverse events (2 with retention secondary to overtightening, one with recurrent UTI secondary to mesh exposure).

The authors concluded, “the tension-free vaginal tape procedure is effective and safe even after 10 years. The objective cure rate is high, but the subjective outcome is significantly lower in mixed urinary incontinence patients compared with patients with pure stress urinary incontinence. Recurrent stress urinary incontinence does not affect the outcome, and tape-related problems are rare.” (International Journal of Urology (2012) 19, 1003–1009)

Nilsson (2013) – Nilsson et al sought to evaluate the long-term effect of the tape material and to assess the continence status 17 years after surgery while evaluating for mesh complications. Objective and subjective continence status was assessed

by a cough stress test and the patient's global impression of improvement as well as by condition-specific quality of life questionnaires. Seventy-eight percent (78%) of the potentially assessable women were evaluated either by a clinic visit or by a telephone interview. One case of a minimal, symptom-free tape extrusion was seen; the patient, aged 69 years, had a small symptom-free exposure of the tape on the right-side peri-urethrally. The woman had not attended the 11-year follow-up visit and at her 7-year visit no tape exposure was seen. Her vaginal mucosa was atrophic and she was prescribed local estrogen therapy. She was continent and highly satisfied with the operation.

No other tape complications occurred. Over 90 % of the women were objectively continent. Eighty-seven percent (87%) were subjectively cured or significantly improved.

The authors concluded, "the TVT operation is durable for 17 years, with a high satisfaction rate and no serious long-term tape-induced adverse effects." (Int Urogynecol J 2013)

Svenningsen (2013) – Svenningsen et al sought to evaluate the long-term objective and subjective outcomes in a patient population 10 years after the retropubic TVT procedure. Over 600 women were identified having a TVT sling placed over a 2-year period by 4 different gynecologic departments. They included 483 women, 327 of which underwent examination in the clinic at a median duration of 10.8 years.

For subjective data, a short-form urinary incontinence disease-specific questionnaire was used. For objective evaluation, the women underwent a valsalva stress test. The objective cure rate was 89.9 %, and the subjective cure rate was

76.1 %. Over 82 % of the patients stated they were “very satisfied” with their surgery while Only 2.3 % of the women had undergone repeat SUI surgery.

The authors concluded that the long-term objective and subjective outcome after retropubic TVT was excellent with a low number of reoperations.

Han (2014) – Han et al sought to evaluate the long-term durability and functional outcomes of TVT and identified the risk factors that may affect recurrence. Cure rates decreased from 96.6 % at 1-year post-surgery to 83.0 % at 5 years. The cure rates between 5 and 12 years were similar (83.0 vs. 79.6 %). Valsalva leak point pressure (VLPP) less than 60 H_2O (indicative of those patients exhibiting intrinsic sphincter deficiency), was the only independent factor that predicted recurrence.

The authors concluded TVT is an effective long-term treatment for SUI, although the cure rate may decrease with time. Intrinsic sphincter deficiency was predictive of SUI recurrence.

Song (2017) – Song et al sought to evaluate the long-term outcomes from the tension-free vaginal tape (TVT) procedure and investigated the data from a minimum 13-year follow-up and predictive risk factors affecting efficacy for treatment of female stress urinary incontinence (SUI). A total of 206 (mean age, 59.2 ± 8.8 years) women who underwent the TVT procedure for SUI were selected and followed. Patients were followed yearly over the 13-year period, and each time were evaluated with a detailed symptom review, stress test, patient global satisfaction questionnaire, uroflowmetry with PVR measurement and examined for post-operative complications associated with the TVT procedure.

The primary outcome measure at 13 years was cure of SUI defined as the absence of any episodes of involuntary urine leakage during stressful activities and a

negative cough stress test. The cough stress test was performed in standing position with a full bladder.

The overall 13-year success rate – a combination of those with complete cure or improved (defined as "a significant reduction of urine leakage, such that no further treatment was required") was 82.5%. No patients were identified over the 13-year study with voiding dysfunction. Only one patient experienced a mesh complication and remained continent following resection.

The authors concluded, "the TVT procedure has a high long-term follow-up success rate ….. No unexpected serious long-term complications after the TVT procedure were identified."

While a 13-year study certainly answers the question of long-term efficacy and safety, due to the TVT being the Gold Standard for the surgical correction of SUI for so many years, we are now seeing data from 17-year studies. Braga et al sought to assess the efficacy and safety of the TVT 17 years post-implantation in the surgical management of their SUI patients. Their study was prospective and all TVT procedures were performed according to the technique originally described by Ulmsten. The study included 52 women with genuine stress urinary incontinence. Women with mixed urinary incontinence were excluded. At 17-year follow-up, almost 90% of the original study group was available for evaluation. Six were lost to follow-up and three had died from medical causes unrelated to their TVT procedure. All women who were lost to follow-up were noted to have been subjectively cured at their last follow-up visit. At 17 years post-surgery, 89% of the participants were subjectively cured of their stress urinary incontinence based on validated questionnaires and 91.3% were objectively cured based on valsalva cough stress test. No patients required resection or release of their sling

over the 17-year period. There were also no mesh erosions and no mesh-related complications over the 17-year follow-up period. While some patients did develop urge urinary incontinence during their 17-year follow up, the authors wisely noted that this observation could simply reflect the aging of the patients rather than a direct consequence of the surgery and went on to conclude that the TVT procedure "is highly effective, safe and has a long-lasting effectiveness over time." (Braga 2018)

Also demonstrating 17-year follow-up was a recently published 2018 article in the International Urogynecology Journal by Bakas et al who sought to assess the outcome of the TVT procedure in patients with stress urinary incontinence. The 17-year follow-up assessment included a gynecologic examination, urinalysis, cough stress test in both the lithotomy and/or upright position, filling and voiding cystometry and uroflow, as well as validated questionnaires. Out of the 61 originally implanted patients, 56 were available for follow-up and showed an objective cure rate of 84% at 17 years with a subjective cure rate of almost 80%. There was one case of TVT mesh exposure which was managed conservatively. No other serious adverse effects were noted in the 17-year follow-up period. The authors concluded, "the TVT procedure for the management of stress urinary incontinence in women maintains its efficacy in the long-term, having an objective cure rate of 83.9% and a subjective cure rate of 78.6% at 17 years follow-up, with a very low complications rate."

The above studies and scores of other well-respected prospective, retrospective and randomized controlled trials, have shown excellent long-term efficacy of both the TVT and TVT-O mid-urethral slings (MUS).

Recently, a Finnish national register examined data from over 38,000 patients and found that synthetic slings like TVT and TVT-O result in fewer re-operations than the older surgeries I've previously discussed (Kurkijarvi 2017).

Compared to a Burch or autologous sling procedure, mid-urethral slings have shown similar or greater efficacy in multiple randomized controlled trials (RCTs) while providing the stress incontinent patient a less invasive surgical treatment option. Plaintiff's Experts have alleged that there are safer alternatives than the TVT, TVT-Exact and TVT-O mid-urethral slings, yet Albo's 2007 RCT found that autologous fascial slings and the Burch procedure have a serious adverse event rate of 13% and 10% respectively.

G. Complications/Safety

Polypropylene, the entity comprising the TVT, TVT-Exact and TVT-O mid-urethral slings, despite assurances from Plaintiff's Counsel, has been shown safe and effective for decades. Prolene polypropylene suture, the entity comprising the matrix of the mid-urethral slings was deemed "safe and effective for use" by the FDA in 1969 (B.H. Minchew, MD, Director of the FDA's Bureau of Medicine). Since that time, polypropylene has been used extensively in urologic and gynecologic surgeries. Multiple other clinical trials have demonstrated the overall safety of type I polypropylene (Rezapour 2001, Ulmsten 2001, Nilsson 2001).

Plaintiff's Counsel have suggested a number of unproven claims of defective design on the part of TVT, TVT-Exact and TVT-O, including cytotoxicity, adverse and prolonged host-tissue response, chronic inflammation, mesh degradation and others.

Cytotoxicity/Adverse Host Tissue Response / Foreign Body Reaction – Claims of a prolonged and adverse tissue response are baseless, as they are extrapolated from animal models or based on studies from different areas of the human body and do not correlate with mesh sling implanted underneath the urethra. As stated above, polypropylene, the entity comprising the TVT family of slings, despite assurances from plaintiff's counsel, has been shown safe and effective for decades.

Chronic Inflammation - Claims that there is an ongoing chronic inflammatory reaction of clinical significance is also baseless. Any foreign object implanted in the body, whether mesh or suture used in native tissue repairs, is expected to cause an inflammatory reaction. Active inflammatory reactions are acute and seen in the post-operative healing phase. There is no legitimate evidence to support the claim of an ongoing, active, and harmful inflammatory reaction in patients receiving mesh.

Mesh Degradation - Any suggestions by Plaintiff's counsel regarding "mesh degradation" are also not supported by reasonable medical literature. We have solid, scientific evidence published in the International Urogynecology Journal that directly contradicts this claim. In Thames study, they found that "cleaning of explanted Prolene meshes and subsequent analyses showed that they did not degrade in vivo, confirming the in vivo stability of properly formulated polypropylene. Instead, the cracked layer that some researchers have identified as degraded Prolene is an adsorbed protein–formaldehyde coating, resulting from the well-established formalin–protein fixation process, which occurs immediately upon placing an explant in formalin." (Thames 2017)

Plaintiff's experts have even claimed bacteria in the vagina "can attach to the mesh and secrete a biofilm or a polysaccharide slime" which "could prevent the host

defensive mechanism from clearing the infection." If this is of legitimate scientific concern, all urologic and gynecologic surgeons should immediately stop performing vaginal surgery where any implant, including suture, is used. The simple fact is if an implant, whether mesh or suture, is implanted in an appropriate (well-estrogenized) patient by a well-trained surgeon, the risk of long-term sequelae is extremely small.

Plaintiff's counsel also suggests that intra-operative and post-operative complications such as decreased sexual function/dyspareunia, exposures, erosions, recurrent UTI, etc. are a direct result of the mesh sling. This is false. These complications are commonly known complications of any pelvic or vaginal surgery and have been discussed for years in pelvic reconstructive circles.

The long-term prevalence of dyspareunia in patients receiving mid-urethral slings for SUI is extraordinarily small. In fact, multiple studies show improvements in sexual function for sexually active patients treated with mid-urethral slings for SUI. (Sexual Activity and Function in Women More Than 2 Years after Mid-urethral Sling Placement. HM Zyczynski, 2012; Sexual Function Following Retropubic TVT and Transobturator Monarc Sling in Women with Intrinsic Sphincter Deficiency: a Multicentre Prospective Study. International Urogynecology Journal February 2012, Volume 23, Issue 2, pp 153–158.**;** The Impact of Mid-urethral Sling Surgery on Sexual Activity and Function in Women With Stress Urinary Incontinence. Mengerink**.** J Sex Med. 2016 Oct;13(10):1498-507.)

I have several patients sent to me on a monthly basis with a diagnosis of recurrent urinary tract infections. The number one cause of recurrent urinary tract infections

I see in this age group is untreated or insufficiently treated vaginal atrophy. The fact that some patients have experienced urinary tract infections following placement of a mid-urethral sling does not indicate a link between the two. Overtightened slings can lead to urinary retention which may place women at an increased risk of UTI, but that remains a function of an improper implantation and not the product itself. We see post-operative, even recurrent UTI, occurring after native tissue POP procedures where mesh is not utilized. To my knowledge, there exists no conclusive scientific evidence that links properly placed mesh implants with recurrent urinary tract infections. Rather, UTIs are extremely common, especially in post-menopausal women, as noted in Haylen's 2009 article.

Exposures of permanent implantable materials are commonly known as potential complications. This is not unique to mesh. Mesh exposure/erosion is a well-known and warned about potential complication following any mesh surgery. In fact, pelvic surgeons have known about this risk for decades, not just in the context of mesh surgeries but also in native tissue repairs which always carry the potential risk of a suture exposure. The overall risk of urethral erosions is very low, estimated at less than 1 in 1000 (Kuuva 2002), with only examples of case reports in the literature. And while Plaintiff's Counsel, through advertisements and scare tactics, would have the general public convinced of the mesh's "ability" to move around the body and wreak havoc, it's simply not the case. The vast majority of mesh exposures are small and asymptomatic. And those that do require treatment are typically easy to resolve in the right hands. As a full-time, practicing Urogynecologist, I remove symptomatic mesh and suture exposures as part of my practice. The overwhelming majority of patients experience a complete resolution of their symptoms following a quick revision procedure. One must also keep in

mind that revision procedures are also necessary, at times, in the non-mesh augmented cases.

In addition to removing mesh exposures and erosions, I also remove exposures and erosions of permanent implantable materials used in native tissue repairs of SUI. I have removed cadaveric exposures from pubovaginal slings, suture exposures from needle urethropexies, and suture erosions from Burch and MMK procedures. Exposures of implantable materials including suture and even biologic materials like cadaveric fascia are well known.

Several papers have detailed cadaveric fascia lata used in pubovaginal slings exposed or eroded following implantation (Amundsen, 2003; Webster, 2003; Kammerer-Doak, 2002; Golomb, 2001; Handa, 1999) According to the highest-level evidence available - systematic reviews and meta-analyses - mesh exposures or erosions following a full-length sling like TVT and TVT-O have an acceptably low rate of occurrence (Cochrane 2015; Shimpf 2014). The fact that erosions can occur does not mean that slings like TVT, TVT-Exact and TVT-O are defectively designed.

A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure was conducted by Kuuva et al in 2002. (*Acta Obstet Gynecol Scand* 2002; 81: 72–77. C Acta Obstet Gynecol Scand). In Kuuva's analysis, the incidence of bladder perforation was 38/1000, intra-operative blood loss over 200 ml 19/1000, major vessel injury 0.7/1000, nerve injury 0.7/1000, vaginal hematoma 0.7/1000 and urethral lesion 0.7/1000. The incidence of minor voiding difficulty was 76/1000, urinary tract infection 41/1000, postoperative urinary retention 23/1000, retropubic hematoma 19/1000, wound infection 8/1000 and vaginal defect healing 7/1000. In that analysis, no case of tape rejection or

life-threatening complication occurred and the incidence of complications requiring laparotomy was quite low 3.4/1000.

Kuuva et al concluded, correctly, that the TVT procedure is a safe method for the treatment of stress urinary incontinence provided that appropriate training is offered. The low risks of complications was later confirmed by Schimpf who, in her meta-analysis, showed acceptably low rates of intra-operative and post-operative complications.

All or some combination of the complications described above are possible complication of pubovaginal fascial slings. All or some combination of the complications described above are possible complication from native tissue Burch urethropexy, native tissue MMK, native tissue Kelly plication, etc. The simple fact of the matter is there remains no available treatment for the surgical management of SUI that, compared to TVT, TVT-Exact or TVT-O, significantly reduces or eliminates potential complications while offering the consistently proven long-term success rates shown in the medical literature. Compared to a Burch or autologous sling procedure, mid-urethral slings have shown similar or greater efficacy while providing the patient a less invasive surgical treatment option. Albo's 2007 RCT found that autologous slings and the Burch procedure have a serious adverse event rate of 13% and 10% respectively, with wound complications in those procedures documented at 25%.

H. FDA Warning

On October 20, 2008, the FDA released a Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in

Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence. In their notification, they stated they had received "over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI." They went on to list complications of infection, pain, urinary problems, recurrence, organ and vessel damage, vaginal scarring, exposure and dyspareunia. Unfortunately, they did so while neglecting to also inform the healthcare practitioners that the exact same complications were known to occur with the alternative procedures of pubovaginal slings, needle urethropexies and native tissue colposuspension (Burch / MMK). They indicated the complications were rare.

The FDA then released another notification in 2011, where they reversed course stating "serious adverse events are NOT rare," a direct contradiction to their original 2008 warning and a direct contradiction to the information offered in multiple systematic reviews and meta-analyses. This update centered more around the use of mesh in POP but made another inaccurate statement when they claimed "transvaginally placed mesh in POP repair does NOT conclusively improve clinical outcomes over traditional non-mesh repair." This statement has been proven false in multiple systematic reviews. Additionally, while the bulk of this update centered around mesh used in POP, they did indicate in the opening paragraph that mesh used in SUI could also lead to "serious adverse events" that were "not rare:" "The FDA also conducted a systematic review of the scientific literature to learn more about the safety and effectiveness of POP and SUI using surgical mesh. The FDA determined that serious adverse events are NOT rare."

I. Responses

Following the inaccurate FDA notification, several responses were generated by profession medical societies who, unlike the FDA panel, were filled with pelvic reconstructive surgeons with decades of experience in research, clinical medicine and surgical correction of SUI.

Most of the early position responses dealt exclusively with mesh utilized in POP repairs (Murphy 2011) as the 2011 FDA notification leaned heavily against mesh for POP. In 2018, the American Urogynecologic Society (AUGS) , in conjunction with the Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) released a joint position statement. In their statement, they discussed the same complications described by the FDA and also discussed the inaccuracies contained in the FDAs white paper and safety communication, even pointing out contradictory statements on the FDA's own website: "The safety and effectiveness of multi-incision slings is well-established…"
The joint AUGS/SUFU panel, comprised of skilled surgeons and researchers infinitely familiar with the workup, diagnosis, non-surgical and surgical treatment of SUI, performed an exhaustive review of the available scientific literature and concluded the following:

1. Polypropylene material is safe and effective as a surgical implant.
2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.
3. Polypropylene mesh mid-urethral slings are a standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.
5. The European Commission enquiry on the safety of surgical meshes supports continuing synthetic sling use for SUI.

Each of these bullets were accompanied by an explanation backed up not only by years of clinical and scientific evidence, but by the FDA's own previous statements. They ended their position statement with the following: "This procedure (mid-urethral sling for SUI) is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence." I agree with these statements.

A list of supporting organizations filled with experienced surgeons and clinical researchers offered their backing of the statement, including The American Association of Gynecological Laparoscopists (AAGL), The American College of Obstetricians and Gynecologists (ACOG), The National Association for Continence (NAFC), International Urogynecological Association (IUGA), and The Society of Gynecologic Surgeons (SGS).

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) also released a position statement in 2018. In it, they state "in the case of SUI and the use of mid-urethral slings, this surgery has been extensively reviewed with numerous high-quality studies. Overall, the safety profile has been found to be very good with high success rates. In most cases, women's quality of life and sexual function improves significantly after this surgical intervention. All surgical procedures have the risk of complications. Overall, mid-urethral slings for SUI has been found to have a lower complication

rate than other surgical procedures performed for female SUI. Other procedures, such as Burch/open colposuspension, urethral injection and suprapubic sling without mesh have been analyzed in the Scottish review. When compared to these procedures, the mid-urethral sling carries a lower overall risk of complications such as recurrent SUI, damage to bladder, difficulty passing urine, excessive bleeding, infection, and pain." I agree with this statement.

Even the FDA changed course again, and in a 2013 FDA update on mesh mid-urethral slings stated, "with the exception of mesh erosion, the above complications [pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring] can occur following a non-mesh surgical repair for SUI." (FDA, Considerations about Surgical Mesh for SUI, 2013). I am in agreement with this statement from the FDA's 2013 communication, with the exception of the exclusion of mesh erosion. Any device, including suture, used in the surgical repair of SUI can lead to exposure or erosion as detailed above.

J. TVT Exact

Building on the success of the original TVT product, Gynecare released the TVT Exact mid-urethral sling in 2010. TVT Exact remains a viable tool in the treatment of stress urinary incontinence even today. Functionally the same product as the original TVT with a slightly reduced diameter trocar, same mesh and same placement, TVT Exact offers surgeons the ability to easily place both trocars utilizing small trocar sheaths, where surgeons can look for evidence of bladder injury on a single cystoscopic pass rather than two or three times, which was the

standard under the original TVT product. This decreases the risk of urethral injury or a bladder injury with multiple cystoscopic passes, which are now unnecessary given the sheath guided entry of the TVT Exact. While the introducing trocar is thinner, the Exact offers the same trocar curvature and the same tip radius. The same edgeless implant sheath over the mesh remains, as does the same laser cut mesh that has been trusted since 2007. Additionally, the procedural steps for placement of the TVT Exact are the same as those procedural steps utilized since the late 1990s with the original TVT. Since TVT Exact is functionally the same product as TVT, when professional statements and studies regarding the TVT procedure are quoted, they are noted by researchers and trained pelvic reconstructive surgeons to remain applicable to the TVT Exact as well.

K. Plaintiff's Expert Witness Opinions/Key Position Statements

Plaintiff's Experts and Counsel build the entirety of their case based on language and statements which are designed to shock but that are not backed up by scientific evidence. One expert's witness summation is as follows: "Ethicon's old construction mesh (Prolene), used in the TVT, is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence because the pores are too small, it is heavy weight mesh, it degrades over time, causes chronic foreign body reactions, fibrotic bridging, mesh contracture / shrinkage, fraying, particle loss, biofilm formation and infections, has sharp edges, ropes, curls and deforms, and the pores collapse with tension."

To address these inaccurate claims, I will present the available scientific evidence and information directly from the FDA, much of which is listed above throughout my statement.

1. Paraphrasing their first statement, they claim prolene mesh used in the TVT is not suitable as an implant because the pore size is too small and the weight of the mesh is too heavy.

   Mesh material is classified into four different categories.

   a. Type I consists of macroporous mesh (eg, Prolene/TVT). The pore size is >75 μm and hence allows infiltration by macrophages, fibroblasts, blood vessels in angiogenesis, and collagen fibers.
   b. Type II consists of microporous mesh (eg, Gore-Tex) and has a smaller pore size of <10 μm.
   c. Type III consists of a macroporous patch with multifilaments or a microporous component (eg, woven Dacron, polypropylene fibrils/IVS Tunneller).
   d. Type IV consists of submicronic pores (eg, Silastic, dura mater substitute).

   The 75 μm+ pore size of the TVT mesh allows infiltration by macrophages, fibroblasts, blood vessels in angiogenesis, and collagen fibers, thus leading to excellent incorporation in to the tissue and making post-operative infections near impossible. There is no clinical evidence that the stiffness and weight of the TVT mesh is flawed. "Gynecare TVT uses a Type I monofilament, macroporous mesh that has been shown to have a unique tensile behavior of low stiffness and easy elongation, a combination which

appears to reduce postoperative complications." (Moldovan 2015). There is no clinical evidence supporting Plaintiff's Counsel claims that a lighter weight, larger pore, partially absorbable mesh would be a safer alternative design. Clinical studies looking at original prolene mesh vs lighter weight meshes in POP studies have shown similar efficacy, as well as similar complication rates between the two.

2. Plaintiff's Expert/Counsel's second statement suggests mesh "degrades over time." This too is patently false. Any suggestions by Plaintiff's counsel regarding "mesh degradation" are not supported by reasonable medical literature. We have solid, scientific evidence published in the International Urogynecology Journal that directly contradicts this claim. In Thames study, they found that "cleaning of explanted Prolene meshes and subsequent analyses showed that they did not degrade in vivo, confirming the in vivo stability of properly formulated polypropylene. Instead, the cracked layer that some researchers have identified as degraded Prolene is an adsorbed protein–formaldehyde coating, resulting from the well-established formalin–protein fixation process, which occurs immediately upon placing an explant in formalin." (Thames 2017)

3. Plaintiff's Expert/Counsel's third statement suggests mesh "causes chronic foreign body reactions, fibrotic bridging, mesh contracture/shrinkage." Claims that the mesh's ongoing foreign body reaction is defective is also baseless. Any foreign object is expected to cause, at a microscopic level, a continuing reaction. The active inflammatory reaction, though, seen after an object like mesh is implanted is acute. There is also no evidence to suggest clinically significant shrinkage. While surgeons place the TVT in a

tension-free fashion anticipating a small degree of contraction, this is something well known to surgeons and, again, not clinically significant. Clinically significant mesh shrinkage in the case of an implanted TVT sling would lead to overtightening under the urethra, translating to urethral obstruction and voiding dysfunction which would be evidenced by increasing post-void residuals (PVR) over time. Nilsson's 17-year follow-up study of TVT looked at the possibility of shrinkage by observing post-void residual volumes and found "there seems to be no shrinkage of the TVT mesh over time, as suggested by PVR volumes within normal ranges, except for 2 patients with concomitant diseases (Parkinson's, grade III cystocele)." Additionally, Lo concluded almost a decade earlier "the observations of the tape position and characteristics suggest that shrinkage and compromise of the TVT sling does not occur. The TVT sling fixes to its original implanted site along the urethra and appears to slowly descend with the surrounding tissue with time. The urethra dynamic kinking contributes to the postoperative urinary continence when the TVT sling is placed at the mid-urethra." (Lo 2004) Around that same time, Dietz's study also concluded "the tension-free vaginal tape does not appear to contract or shorten over time. On the contrary, it appears to slowly migrate caudally relative to the symphysis pubic, together with the surrounding tissues. Per year, this "give" amounts to approximately 1.5 mm. As surrounding tissues are displaced at a very similar rate, this seems to indicate that the tape moves with the prolapse rather than signifying true "migration". Tape mobility on Valsalva, a measure of elasticity, remains largely unchanged *(translabial ultrasound)."* (Dietz 2003). Lukacz's 2002 study gave further scientific evidence against the claim of "shrinkage," showing that unchanged resting Q-tip angles

measured during the first year post-operatively confirmed the tension-free concept and demonstrated no shrinkage or tightening of the sling.

4. Plaintiff's Expert/Counsel's fourth statement suggests "fraying and particle loss." There are no scientific studies that have shown clinically significant evidence of particle loss and/or fraying of mesh in vivo. I have removed numerous pieces of mesh over my career. Mesh incorporated in to the tissues does not undergo these distortions. We as surgeons are likely guilty of causing damage and fraying when we attempt to remove improperly placed meshes that have caused complications. Those specimens viewed under microscopy following implant may show evidence of fraying but that is a result of our manipulation of the material during explant.

5. Plaintiff's Expert/Counsel's fifth statement suggests "biofilm formation and infections can attach to the mesh and secrete a biofilm or a polysaccharide slime" which "could prevent the host defensive mechanism from clearing the infection." As stated before, if this is of legitimate scientific concern, all urologic and gynecologic surgeons should immediately stop performing vaginal surgery where any implant, including suture, is used. The simple fact is if an implant, whether mesh or suture, is implanted in an appropriate (well-estrogenized) patient by a well-trained surgeon, the risk of long term sequelae, including infection, is extremely small.

6. Plaintiff's Expert/Counsel's sixth statement suggests the polypropylene mesh "has sharp edges, ropes, curls and deforms and the pores collapse with tension." As stated above, the 75 μm+ pore size of the TVT mesh allows infiltration by macrophages, fibroblasts, blood vessels in angiogenesis, and

> collagen fibers, thus leading to excellent incorporation into the tissue. Once incorporated into the tissue, and if properly inserted into a correctly dissected field, the mesh cannot rope, curl, deform or undergo "pore collapse." Again, the Plaintiff's Expert statements are unsupported by medical literature. Other often-mentioned design defects of "roping," "curling," and "banding" are not related to the implant itself – but, rather related directly to improper placement of said product. Based on my vast clinical experience and constant review the medical literature, I have seen no evidence that any of these alleged defects or characteristics of the mesh have any clinical significance - if they occur at all.

Many Plaintiff's Experts have also stated that the laser cut mesh used in Ethicon's newer slings is too heavy and too stiff for implantation in vaginal tissue, despite the fact that hundreds of thousands of women have had laser cut slings placed since 2010 without complications. Rusavy looked at this very debate in his study published in the International Urogynecology Journal in 2017. Rusavy conducted a retrospective analysis of clinical and ultrasound data available on women who had undergone placement of mechanically cut TVT-O mid-urethral slings and women who had undergone placement of laser cut TVT-O mid-urethral slings. Post-operative evaluations utilizing clinical examination, urodynamics and ultrasound were undertaken and validated questionnaires were used for subjective data. Ultrasound evaluations were conducted at day 1, week 2, month 3 and 1 and 2 years following implant. Dr. Rusavy found that no differences were noted between the two groups with respect to bladder neck mobility, showing that the direction and length of vector of the movement of the bladder neck between rest and maximal valsalva between the mechanical cut and laser cut groups were that same. While some differences were noted in mobility of the slings between groups on

day 1 and week 2, no differences were noted from the 3 month visit onward (differences in movement could be expected during the first couple months during healing and incorporation). The study also found that the long-term subjective and objective surgery outcome measures (including cure rates, reoperation and mesh exposures) at 2 years after the surgery were comparable. Ultimately, the authors concluded that, "the long-term follow-up outcome and ultrasound data presented in this study suggest that the importance of the tape resistance to elongation under load is of significance only in the first 2 weeks after implantation." So, while some differences may exist at the microscopic and biomechanical levels, they are inconsequential when evaluating safety and efficacy, as all outcome measures between the groups were similar.

Some Plaintiffs' experts claim that "many of these [mesh] complications are life-altering and permanent, unlike those seen with traditional repairs." There is no valid scientific evidence to back up this claim. I have personally corrected complications from native tissue repairs that caused horrible dyspareunia, pelvic pain, levator ani spasm, depression and a myriad of other complaints. Any vaginal surgery, mesh-augmented or native tissue in nature, can lead to life-altering, prolonged complaints. This is a basic tenet of vaginal surgery. The inherent risks of vaginal pain, vaginal scarring, dyspareunia, contraction, infection, recurrence and exposures of implantable material have been common knowledge among gynecologic and urologic surgeons for decades. The implementation of the use of mesh to augment prolapse and incontinence repairs and decrease recurrences did not change this. The risks noted above - vaginal pain, vaginal scarring, dyspareunia, contraction, infection, recurrence and exposures of implantable material - are discussed on a near daily basis with medical students and OB/GYN residents on my Urogynecology rotation and elective at our academic medical

center. Residents, even medical students, are taught from their first day on service, the inherent risks of any vaginal surgery. These same principles were taught to me as a medical student, reinforced ad nauseum as a medical resident, and further discussed during my fellowship. No surgeon performing gynecologic procedures of this magnitude can claim they are unaware that making any incision in the vaginal epithelium of a woman can lead to scarring, pain, dyspareunia, infection, recurrence or exposures. This is as basic as Foley catheter management and should be expected knowledge of any gynecologic surgeon. In addition to everyday teaching of these basic tenets during training, a mountain of scientific literature has echoed the same, putting gynecologic surgeons on notice regarding complications possible in vaginal surgeries for literally decades. (Dyspareunia Following Vaginal Surgery, Francis, 1961; Repair of post-hysterectomy vaginal-vault prolapse, Lane, 1962; Sexual life after gynaecological operations—II, Amias, 1975; The complications of colposuspension, Galloway, 1987; Influence of operations for Stress Incontinence and/or Genital Descensus on sexual life, Haase, 1988; Rectocele Repair; Four years' experience, Arnold, 1990; Pelvic Support Defects and visceral and sexual function in women treated with sacrospinous ligament suspension and pelvic reconstruction, Paraiso, 1996; Banked human fascia lata for the suburethral sling procedure: a preliminary report, Handa, 1996; Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation, Benson, 1996; Posterior colporrhaphy: its effects on bowel and sexual function, Khan, 1997; A new operation for genitourinary prolapse, Nicita, 1998; Should sacrospinous ligament fixation for the management of pelvic support defects be part of a residency program procedure? The University of Miami experience, Penalver, 1998; Failure of allograft suburethral slings, Fitzgerald, 1999; Complications of surgery of genuine stress incontinence, Chaliha, 1999; Erosion of fascial sling in to

the urethra, Handa, 1999; Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence, Weber, 2000; Management of urethral erosion caused by a pubovaginal sling, Golomb, 2001; Pubovaginal sling using cadaveric fascia and bone anchors: disappointing early results, Carbone, 2001; Vaginal erosion of cadaveric fascia lata following abdominal sacrocolpopexy and suburethral sling urethropexy, Kammerer-Doak, 2002; Urethral erosion following autologous rectus fascial pubovaginal sling, Webster, 2003; TVT, TVT-O, Gynemesh, Prolift IFU; 2000 TVT Surgeon Monograph; Prolift Surgical Technique Guide; 2007 Prolift Surgeon Monograph; TVT, TVT-O, Gynemesh and Prolift Profession educational materials)

On occasion, plaintiff experts have alleged that polypropylene mesh causes cancer. This accusation lacks any support in the medical literature and is baseless.

V. CONCLUSIONS

Stress urinary incontinence has always been a common problem among women. It often has a serious and devastating impact on a woman's quality of life. Slings like TVT, TVT Exact and TVT-O revolutionized the treatment of this condition.

A macroporous, monofilament polypropylene graft, as used in the Ethicon TVT products is safe and effective, as demonstrated by the highest level of clinical evidence. These polypropylene mesh grafts have been utilized extensively since the 1990's by a combination of gynecologic and urologic surgeons in the treatment of urinary incontinence. Mesh grafts have been used extensively in general surgery, having been the mainstay for abdominal hernia repairs in excess of 70

years, with polypropylene meshes being utilized for over 5 decades. Type 1 polypropylene mesh (used in the TVT graft), due to its monofilament makeup and large pore size, has the highest biocompatibility and lowest risk of infection compared to other mesh types (Ford Cochrane Review 2015). With the macroporous design, the risk of chronic infection is quite low, as blood vessels and macrophages can easily enter the available spaces to combat potential infectious processes. Between my use of polypropylene meshes used in prolapse and incontinence repairs, I have placed mesh in roughly 2500-3000 women. In that group, I have experienced very low rates of complications following mesh surgery and instead have seen high efficacy rates.

Compared to a Burch or autologous sling procedure, mid-urethral slings have shown similar or greater efficacy while providing the patient a less invasive surgical treatment option (Albo et al. 2007). This same RCT found that autologous slings and the Burch procedure have a serious adverse event rate of 13% and 10% with wound complications near 25%. Long-term efficacy for the Burch colposuspension has been found to diminish over time, with one study finding a 77.4% cure rate at 4.5 years (Demirci 2001) and while another found a cure rate of 63% at 6 years (Kjolhede 1994). On the other hand, long term studies demonstrate the safety and efficacy of slings like TVT. These devices have been evaluated in over 2,000 studies and approximately 200 randomized controlled trials. Systematic reviews (Ford Cochrane Review 2015; Tommaselli 2015) and meta-analyses (Schimpf 2014) confirm their safety and efficacy. Mid-urethral slings show similar or high efficacy rates compared to the more invasive Burch and fascial sling procedures. While some meta-analyses have shown mid-urethral slings demonstrated a higher rate of bladder perforations, those are easily managed at the time of the procedure, with little to no long-term sequalae, compared to the

more common complications from Burch and fascial slings of voiding dysfunction, de novo urge urinary incontinence and significant lower urinary tract symptom which are typically long-term and can be quite disabling for patients.

TVT is a state of the art product whose benefits outweigh the risks. Implanting TVT to treat SUI has been the standard of care since its introduction in 1998. I'm aware of no alternative surgery or design that has been shown to significantly reduce or eliminate potential complications like those targeted by Plaintiff's Experts/Counsel. Experts for the Plaintiff have alleged various design defects in TVT, such as particle loss, cytotoxicity, degradation, roping, curling, banding, fraying, stiffness, pore size, weight of the mesh and even cancer. Based on my experience and constant review of the medical literature, I've seen no evidence that any of these alleged defects or characteristics of the mesh have any clinical significance, if they happen at all. Claims that the mesh's ongoing foreign body reaction is defective is also baseless. Any foreign object is expected to cause at a microscopic level a continuing reaction. The active inflammatory reaction, though, seen after an object like mesh is implanted is acute. Experts for plaintiffs have also claimed that laser and mechanically cut mesh both cause erosions and are therefore defective. These opinions lack merit as there is no published study I know of that establishes a clinical difference between the two. In fact, a recent study found the opposite (Rusavy 2017).

The allegations of Experts for Plaintiffs are unsupported by the medical literature and my clinical experience, and diverge from the conclusions of the leading professional societies that have addressed the safety and efficacy of full length mid-urethral slings like TVT, TVT Exact and TVT-O. Just this year,

AUGS/SUFU updated their position statement which affirmed that polypropylene is a safe and effective implant material, that the MUS is the most extensively studied anti-incontinence procedure in history, and that the MUS "represents the most important advancement in the treatment of stress urinary incontinence in the last 50 years." See also American Urological Association 2013; NICE 2013; International Continence Society 2013; IUGA 2014; ACOG Practice Bulletin 2015; AUA / SUFU 2017. I'm in agreement with these statements.

Experts for Plaintiffs have also claimed that the Burch procedure or other surgeries would be a safer alternative design to TVT. This is simply not the case. Alternative surgeries, suggested as "safer" by Plaintiff's Counsel, are not medical devices and therefore can't be suggested a "safer alternative design." No mesh is available that is more efficacious than TVT's Prolene mesh while still presenting a similarly low risk of complications. Claims that a partially absorbable mesh that is lighter in weight would be a safer design are also not only unsupported by the medical literature; in fact, they are refuted by it. To put a finer point on it, I'm not aware of any mesh available today that would eliminate or significantly reduce complications like erosion, pain, recurrence and dyspareunia - complications that can happen regardless of the material or route utilized. In fact, the only study that has evaluated Ultrapro mesh used as a sling for SUI repair found that an exposure happened in that arm of the study (Okulu).

Ultimately, the onus falls to the physician to make the final decision on whether or not they should be performing any pelvic organ prolapse or anti-incontinence procedure - whether mesh-augmented or not. The inherent risks of vaginal pain, vaginal scarring, dyspareunia, contraction and exposures of implantable material

have been common knowledge among gynecologic and urologic surgeons for decades. The implementation of the use of mesh to augment prolapse and incontinence repairs and decrease recurrences did not change that. Pelvic floor surgeons must rely on their education, training, review of the medical literature and most importantly their experience, knowledge, and skill as a surgeon in treating their patients. Gynecologic surgeons are responsible for understanding pelvic anatomy, proper dissection techniques, and the inherent risks of performing gynecologic surgery, regardless of the use or non-use of polypropylene mesh. Post-operative complications of pain, exposure of implanted materials, urgency, frequency, dysuria, bleeding, discharge, dyspareunia, recurrence, voiding dysfunction, and damage to nerves and vasculature are not unique to mesh implant cases and are inherently seen in various obstetric, gynecologic, and urologic procedures that are commonly performed. Surgeons are expected to understand these risks from day one of their residency training.

The TVT, TVT-O and TVT Exact Instructions For Use (IFU) are not misleading and adequately warned of the potential complications that could follow. Ethicon's professional education information also provided additional information about how to implant these products and its potential complications. As I've previously noted, warnings that Experts for Plaintiffs claim should have been in the IFU (i.e. frequency and severity information regarding mesh extrusions, recurrence, mesh revision procedures, dyspareunia, chronic foreign body reactions, and pelvic pain) were published in peer-reviewed medical literature and were commonly known amongst pelvic floor surgeons years before TVT was cleared by the FDA in 1998. Accordingly, there was no need to warn about these risks in TVTs' IFU. In other words, the TVT products' IFU didn't omit any complications that were unique to it. Risks of pain, scarring, dyspareunia, tissue contraction, recurrence and erosion

have been matters of common knowledge for decades as potential complications stemming from vaginal surgery. Pelvic floor surgeons understand these complications based on their education, training, experience, ongoing review of medical literature, and practice guidelines (AUGS; ABOG / ABU; ACOG). Even residents and fellows are expected to know about these elemental risks of pelvic surgery and to be able to counsel patients accordingly.

The use of TVT, TVT Exact and TVT-O in the treatment of patients suffering from stress urinary incontinence is appropriate and within the standard of care. The products are not defective and work as intended to address complaints of stress urinary leakage, within the given limitations and risks of procedures for SUI. The TVT systems are safe and effective as demonstrated by the highest level of clinical evidence.

I hold the above opinions to a reasonable degree of medical and scientific certainty. All opinions have been compiled based on my education, training and professional experience as a gynecologic surgeon. Additionally, I utilize my significant background in evaluating, diagnosing and treating women with pelvic floor pathologies, annual participation in national and international meetings on women's pelvic health, as well as an extensive review of the available medical literature as it pertains to incontinence treatment, including surgical and non-surgical strategies. I reserve my right to amend or supplement this opinion based on new information that becomes available.

C. Bryce Bowling, MD, FACOG, FPMRS, FACS

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